PATENT APPLICATION

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SYSTEM AND METHOD FOR PROVIDING ELECTRICAL PULSES TO THE VAGUS NERVE(S) TO PROVIDE THERAPY FOR OBESITY, EATING DISORDERS, NEUROLOGICAL AND NEUROPSYCHIATRIC DISORDERS WITH A STIMULATOR, COMPRISING BI-DIRECTIONAL COMMUNICATION AND NETWORK CAPABILITIES

FIELD OF INVENTION

The present invention relates to providing pulsed electrical stimulation for medical therapy, more specifically a system and method for providing electrical pulses to one or both vagus nerve(s) of a patient to provide therapy for obesity, eating disorders, neurological and neuropsychiatric disorders using an implanted pulse generator/stimulus-receiver, having bi-directional communication and networking capabilities.

BACKGROUND

Obesity results from excessive accumulation of fat in the body. It is caused by ingestion of greater amounts of food than can be used by the body for energy. The excess food, whether fats, carbohydrates, or proteins, is then stored almost entirely as fat in the adipose tissue, to be used later for energy. There can be various causes of obesity including, psychogenic, neurogenic, genetic, and other metabolic related factors. Treatment of obesity depends on decreasing energy input below energy expenditure. Treatment has included among other things, various drugs, starvation and even stapling or surgical resection of a portion of the stomach.

The vagus nerve (which is the 10th cranial nerve) plays a role in mediating afferent information from the stomach to the satiety center in the brain. Afferent neuromodulation of the vagus nerve has also shown to have clinical efficacy for various neurological and neuropsychiatric disorders, such as partial complex epilepsy, generalized epilepsy, Parkinsonson's disease, migraines, depression, Alzheimer's disease, anxiety disorders, obsessive compulsive disorders, and the like. The vagus nerve arises directly from the brain, but unlike other cranial nerves extends well beyond the head. At its farthest extension it reaches the lower parts of the intestines. FIG. 1 shows simplified partial innervation of the vagus nerve and FIG. 2 depicts visceral innervation of the vagus nerve in more detail. Since vagus nerve(s) 54 extend to the sub-diaphragmatic region, they can be selectively stimulated from the anywhere along their length, as described later.

Observations on the profound effects of electrical stimulation of the vagus nerve on central nervous system (CNS) activity extends back to the 1930's. In 1988 it was reported in the *American Journal of Physiology*, that the afferent vagal fibers from the stomach wall increased their firing rate when the stomach was filled. One way to look at this regulatory process is to imagine that the drive to eat, which may vary rather slowly with the rise and fall of hormone Leptin, is inhibited by satiety signals that occur when we eat and begin the digestive process (i.e., the prandial period). As shown schematically in the top part of FIG. 3, these satiety signals both terminate the meal and inhibit feeding for some time afterward. During this postabsorptive (fasting) period, the satiety signals slowly dissipate until the drive to eat again takes over

The regulation of feeding behavior is a complex process, and involves the concentrated action of several satiety signals such as gastric distention, the release of the gastrointestinal peptide cholecystokinin (CCK), and the release of the pancreatic hormone insulin. The stomach wall is richly innervated by mechanosensory axons, and most of these ascend to the brain via the vagus nerve 54. The vagus sensory axons activate neurons in the Nucleus of the Solitary Tract in the medulla of the brain (described later in this application). These signals inhibit feeding behavior. In a related mechanism, the peptide CCK is released in response to stimulation of the intestines by certain types of food, especially fatty ones. CCK

reduces frequency of eating and size of meals. As shown schematically in FIG. 4, both gastric distension and CCK act synergistically to inhibit feeding behavior.

Accordingly, appropriate extra-physiologic electrical stimulation of a vagus nerve 54 or both vagus nerves, from just above the stomach level, should produce appetite suppression by causing the patient to experience satiety. This is shown schematically in FIG. 5A in the form of subdiaphramatic bilateral stimulation. FIGS. 5B-5E show the same concept in alternative embodiments. For example, in FIG. 5B is shown bilateral subdiaphramatic stimulation using two separate pulse generators. FIG. 5C shows supradiaphramatic bilateral stimulation using two separate implanted stimulators. FIG. 5D shows unilateral stimulation, and FIG. 5E shows gastric stimulation. All of these embodiments are considered within the scope of this disclosure.

In one aspect, upon experiencing the compulsive craving, the obese patient can voluntarily activate the stimulus generator by activating a predetermined program. In another aspect, the patient receives chronic stimulation according to a predetermined program whereby stimulation is on for a period of time, followed by off-time in repeating cycles

Prior art search discloses essentially "cardiac pacemaker-like" technology applied to stimulating a vagus nerve. U.S. Patents 5,188,104 and 5,263,480 both granted to Wernicke et al. are generally directed to treatment of eating disorders by nerve stimulation. U.S. Patents 4,702,254, 4,867,164, and 5,025,807, granted to Zabara are generally directed to neurological disorders. Such system and method, though convenient has the disadvantage that the internal battery will not last for a desired period of time, which can lead to repeated surgeries for pulse generator replacement. Also, because of the concern for reasonable battery longevity, optimal therapy of giving electrical pulses is usually not utilized, since that would lead to excessive drain on the battery. Further, the programming of the stimulation parameters is performed by the medical staff and requires a visit to the physician's office or the clinic, when a program change has to be made. Thus, the prior art has a cumbersome process of adjusting the therapy levels, in addition to the short battery life.

An inductively coupled system and method for neuromodulation granted to Boveja (one of the inventors of the instant application) U.S. Patents 6,205,359 B1,

6,269,270 B1, and 6,356,788 B2 overcomes many of the disadvantages of an IPG system such as battery life, and easier activation of programs by the patient, but patient convenience remains an issue since a secondary coil has to be kept in close proximity to an implanted primary coil. It would be ideal to have the advantages of both an IPG system and an inductively coupled system. The system and method disclosed, provides an improved method and system for adjunct therapy by providing a system that has the benefits of both systems, and has additional synergistic benefits not possible in the prior art.

The current application discloses an implantable medical device capable of being used as a programmable implanted pulse generator (IPG), or as a stimulus-receiver for an inductively coupled system with power being supplied by an external stimulator 42, as is shown in FIG. 6. In the bottom right part of FIG. 6, is depicted the programming of the implanted stimulator 75 via a programmer 85. Once programmed, the implanted stimulator 75 functions on its own, as shown on the top part of the figure. As shown in the lower left part of FIG. 6, in the other mode of operation the implanted system 75 can be used as a stimulus-receiver where the power is being supplied from an external stimulator unit 42. In this system and method, the patient can choose when to use an external inductively coupled system to conserve the battery life of the implanted module and receive higher levels of therapy, or be stimulated by the internal system for convenience.

FIG. 7 shows a close up view of the implanted stimulator 75, showing the two subassemblies 68, 70. The two subassemblies are the stimulus-receiver module 68 and the battery operated pulse generator module 70. The external stimulator 42, and programmer 85 also being remotely controllable from a distant location via the internet. Controlling circuitry means within the device, makes the inductively coupled stimulator and the IPG operate in harmony with each other, as described later. For example, when stimulation is applied via the inductively coupled system, the battery operated portion of the stimulator is triggered to go into the "sleep" mode. Conversely, when programming pulses (which are also inductively coupled) are being applied to the implanted battery operated pulse generator, the inductively coupled stimulation circuitry is disconnected.

In the system and method of the current invention, after the system is implanted in the patient, optimal stimulation parameters are "titrated" for the

condition of the individual patent. Clinical research has shown that each patient is biologically unique and responds little bit differently to given stimulation. The inductively coupled stimulation part of the system is a very convenient method of adjusting the parameters for stimulation therapy, that would be optimally suited for each individual patient. Further, as depicted in FIG. 8, the external stimulator 42 has a telemetry module and can be controlled remotely via the internet. In one embodiment, numerous pre-determined programs are pre-packaged into the memory of the external stimulator 42. A physician or medical personnel situated remotely is able to selectively activate (and de-activate) selected pre-packaged (pre-determined) programs. As shown in FIGS. 9A and 9B, the telemetry module within the external stimulator wirelessly communicates with a base station 2, either via an attachment as shown in FIG. 9A, or directly as shown in FIG. 9B. Also, as shown in FIG. 10, a physician in a remote location is able to interrogate and selectively program the external stimulator 42 via a server 130.

Once the appropriate stimulation parameters are determined by "trial and error", the battery operated portion of the implanted pulse generator 70 can be programmed to the optimal electrical stimulation parameters via a programmer 85. For ideal therapy, the electrical stimulation parameters need to be adjusted at regular intervals taking into account optimal benefits.

Another distinct advantage of the current system is that when the stimulation is performed via the external stimulator 42, the battery of the implanted pulse generator (IPG) 70 is conserved, extending the life of the implanted system 75.

Background of neuromodulation

The 10^{th} cranial nerve in the body, or the vagus nerve plays a role in mediating afferent information from visceral organs to the brain. The vagus nerve arises directly from the brain, but unlike the other cranial nerves extends well beyond the head. At its farthest extension it reaches the lower parts of the intestines. The vagus nerve provides an easily accessible, peripheral route to modulate central nervous system (CNS) function. In the human body there are two vagal nerves (VN), the right VN and the left VN. Each vagus nerve is encased in the carotid sheath along with the carotid artery and jugular vein. The innervation of the right and left vagus nerves is different. The innervation of the right vagus nerve is such

that stimulating it at the level of the neck, results in profound bradycardia (slowing of the heart rate). The left vagus nerve has some innervation to the heart, but mostly innervates the visceral organs such as the gastrointestinal tract. It is known that stimulation of the left vagus nerve does not cause substantial slowing of the heart rate or cause any other significant deleterious side effects, even when stimulating at the level of the neck.

One of the fundamental features of the nervous system is its ability to generate and conduct electrical impulses. Most nerves in the human body are composed of thousands of fibers of different sizes. This is shown schematically in FIG. 11. The different sizes of nerve fibers, which carry signals to and from the brain, are designated by groups A, B, and C. The vagus nerve, for example, may have approximately 100,000 fibers of the three different types, each carrying signals. Each axon or fiber of that nerve conducts only in one direction, in normal circumstances. Vagus nerve is composed of 80% afferent sensory fibers carrying information to the brain from the head, neck, thorax, and abdomen.

In a cross section of peripheral nerve it is seen that the diameter of individual fibers vary substantially, as is shown schematically in FIG. 12. The largest nerve fibers are approximately 20 μm in diameter and are heavily myelinated (i.e., have a myelin sheath, constituting a substance largely composed of fat), whereas the smallest nerve fibers are less than 1 μm in diameter and are unmyelinated.

The diameters of group A and group B fibers include the thickness of the myelin sheaths. Group A is further subdivided into alpha, beta, gamma, and delta fibers in decreasing order of size. There is some overlapping of the diameters of the A, B, and C groups because physiological properties, especially in the form of the action potential, are taken into consideration when defining the groups. The smallest fibers (group C) are unmyelinated and have the slowest conduction rate, whereas the myelinated fibers of group B and group A exhibit rates of conduction that progressively increase with diameter.

Nerve cells have membranes that are composed of lipids and proteins, and have unique properties of excitability such that an adequate disturbance of the cell's resting potential can trigger a sudden change in the membrane conductance. Under resting conditions, the inside of the nerve cell is approximately - 90 mV relative to the

outside. The electrical signaling capabilities of neurons are based on ionic concentration gradients between the intracellular and extracellular compartments. The cell membrane is a complex of a bilayer of lipid molecules with an assortment of protein molecules embedded in it, separating these two compartments. Electrical balance is provided by concentration gradients which are maintained by a combination of selective permeability characteristics and active pumping mechanism.

The lipid component of the membrane is a double sheet of phospholipids, elongated molecules with polar groups at one end and the fatty acid chains at the other. The ions that carry the currents used for neuronal signaling are among these water-soluble substances, so the lipid bilayer is also an insulator, across which membrane potentials develop. In biophysical terms, the lipid bilayer is not permeable to ions. In electrical terms, it functions as a capacitor, able to store charges of opposite sign that are attracted to each other but unable to cross the membrane. Embedded in the lipid bilayer is a large assortment of proteins. These are proteins that regulate the passage of ions into or out of the cell. Certain membrane-spanning proteins allow selected ions to flow down electrical or concentration gradients or by pumping them across.

These membrane-spanning proteins consist of several subunits surrounding a central aqueous pore. Ions whose size and charge "fit" the pore can diffuse through it, allowing these proteins to serve as ion channels. Hence, unlike the lipid bilayer, ion channels have an appreciable permeability (or conductance) to at least some ions. In electrical terms, they function as resistors, allowing a predicable amount of current flow in response to a voltage across them.

A nerve fiber can be excited by increasing the electrical charge within the neuron, thus increasing the membrane potential inside the nerve with respect to the surrounding extracellular fluid. The threshold stimulus intensity is defined as that value at which the net inward current (which is largely determined by Sodium ions) is just greater than the net outward current (which is largely carried by Potassium ions), and is typically around -55 mV inside the nerve cell relative to the outside (critical firing threshold). If however, the threshold is not reached, the graded depolarization will not generate an action potential and the signal will not be propagated along the axon. This fundamental feature of the nervous system i.e., its ability to generate and

conduct electrical impulses, can take the form of action potentials, which are defined as a single electrical impulse passing down an axon. This action potential (nerve impulse or spike) is an "all or nothing" phenomenon, that is to say once the threshold stimulus intensity is reached, an action potential will be generated.

FIG. 13A illustrates a segment of the surface of the membrane of an excitable cell. Metabolic activity maintains ionic gradients across the membrane, resulting in a high concentration of potassium (K^+) ions inside the cell and a high concentration of sodium (Na^+) ions in the extracellular environment. The net result of the ionic gradient is a transmembrane potential that is largely dependent on the K^+ gradient. Typically in nerve cells, the resting membrane potential (RMP) is slightly less than 90 mV, with the outside being positive with respect to inside.

To stimulate an excitable cell, it is only necessary to reduce the transmembrane potential by a critical amount. When the membrane potential is reduced by an amount ΔV, reaching the critical or threshold potential (TP); Which is shown in FIG. 13B. When the threshold potential (TP) is reached, a regenerative process takes place: sodium ions enter the cell, potassium ions exit the cell, and the transmembrane potential falls to zero (depolarizes), reverses slightly, and then recovers or repolarizes to the resting membrane potential (RMP).

For a stimulus to be effective in producing an excitation, it must have an abrupt onset, be intense enough, and last long enough. These facts can be drawn together by considering the delivery of a suddenly rising cathodal constant-current stimulus of duration d to the cell membrane as shown in FIG. 13B. Cell membranes can be reasonably well represented by a capacitance C, shunted by a resistance R as shown by a simplified electrical model in FIG. 13C.

When the stimulation pulse is strong enough, an action potential will be generated and propagated. Immediately after the spike of the action potential there is a refractory period when the neuron is either unexcitable (absolute refractory period) or only activated to sub-maximal responses by supra-threshold stimuli (relative refractory period). The absolute refractory period occurs at the time of maximal Sodium channel inactivation while the relative refractory period occurs at a later time when most of the Na^+ channels have returned to their resting state by the voltage activated K^+ current. The refractory period has two important implications for

action potential generation and conduction. First, action potentials can be conducted only in one direction, away from the site of its generation, and secondly, they can be generated only up to certain limiting frequencies.

These electrical signals travel along the nerve fibers. The information in the nervous system is coded by frequency of firing rather than the size of the action potential. In terms of electrical conduction, myelinated fibers conduct faster, are typically larger, have very low stimulation thresholds, and exhibit a particular strength-duration curve or respond to a specific pulse width versus amplitude for stimulation, compared to unmyelinated fibers. The A and B fibers can be stimulated with relatively narrow pulse widths, from 50 to 200 microseconds (μs), for example. The A fibers conduct slightly faster than the B fibers and have a slightly lower threshold. The C fibers are very small, conduct electrical signals very slowly, and have high stimulation thresholds typically requiring a wider pulse width (300-1,000 μs) and a higher amplitude for activation. Because of their very slow conduction, C fibers would not be highly responsive to rapid stimulation. Selective stimulation of only A and B fibers is readily accomplished. The requirement of a larger and wider pulse to stimulate the C fibers, however, makes selective stimulation of only C fibers, to the exclusion of the A and B fibers, virtually unachievable in as much as the large signal will tend to activate the A and B fibers to some extent as well.

As shown in FIG. 14, when the distal part of a nerve is electrically stimulated, a compound action potential is recorded by an electrode located more proximally. A compound action potential contains several peaks or waves of activity that represent the summated response of multiple fibers having similar conduction velocities. The waves in a compound action potential represent different types of nerve fibers that are classified into corresponding functional categories as shown in the Table one below,

Table 1

Fiber Type	Conduction Velocity (m/sec)	Fiber Diameter (μm)	Myelination
A Fibers			
Alpha	70-120	12-20	Yes
Beta	40-70	5-12	Yes
Gamma	10-50	3-6	Yes
Delta	6-30	2-5	Yes
B Fibers	5-15	<3	Yes
C Fibers	0.5-2.0	0.4-1.2	No

For many of the applications of the current patent application, it is the slow conduction C-fibers that are stimulated by the pulse generator. The modulation of a nerve in the periphery, as done by the body, in response to different types of pain is illustrated schematically in FIGS. 15 and 16. As shown schematically in FIG. 15, the electrical impulses in response to acute pain sensations are transmitted to brain through peripheral nerve and the spinal cord. The first-order peripheral neurons at the point of injury transmit a signal along A-type nerve fibers to the dorsal horns of the spinal cord. Here the second-order neurons take over, transfer the signal to the other side of the spinal cord, and pass it through the spinothalamic tracts to thalamus of the brain. Of relevance to most therapy applications, and as shown in FIG. 16, duller and more persistent pain travels by another-slower route using unmyelinated C-fibers. This route made up from a chain of interconnected neurons, which run up the spinal cord to connect with the brainstem, the thalamus and finally the cerebral cortex. The autonomic nervous system also senses pain and transmits signals to the brain using a similar route to that for dull pain.

Vagus nerve stimulation, as performed by the system and method of the current patent application, is a means of directly affecting central function. As shown in FIG. 17, nerves have both afferent pathways 19 (inward conducting nerve fibers which convey impulses toward the brain) and efferent pathways 21 (outward

conducting nerve fibers which convey impulses to an effector). The vagus nerve is composed of somatic and visceral afferents and efferents. Vagus nerve is composed of 80% afferent sensory fibers carrying information from the head, neck, thorax, and abdomen to the brain. The sensory afferent cell bodies of the vagus reside in the nodose ganglion and relay information to the nucleus tractus solitarius (NTS). Usually, nerve stimulation activates signals in both directions (bi-directionally). It is possible however, through the use of special electrodes and waveforms, to selectively stimulate a nerve in one direction only (unidirectionally). The vast majority of vagus nerve fibers are C fibers, and a majority are visceral afferents having cell bodies lying in masses or ganglia in the skull.

In considering the anatomy, the vagus nerve spans from the brain stem all the way to the splenic flexure of the colon (also shown in FIG. 2). Not only is the vagus the parasympathetic nerve to the thoracic and abdominal viscera, it is also the largest visceral sensory (afferent) nerve. Sensory fibers outnumber parasympathetic fibers four to one. In the medulla (at the brainstem level), the vagal fibers are connected to the nucleus of the tractus solitarius (visceral sensory), and three other nuclei. The central projections terminate largely in the nucleus of the solitary tract, which sends fibers to various regions of the brain (e.g., the thalamus, hypothalamus and amygdala).

As shown in FIG. 18, the vagus nerve emerges from the medulla of the brain stem dorsal to the olive as eight to ten rootlets. These rootlets converge into a flat cord that exits the skull through the jugular foramen. Exiting the Jugular foramen, the vagus nerve enlarges into a second swelling, the inferior ganglion.

In the neck, the vagus lies in a groove between the internal jugular vein and the internal carotid artery. It descends vertically within the carotid sheath, giving off branches to the pharynx, larynx, and constrictor muscles. From the root of the neck downward, the vagus nerve takes a different path on each side of the body to reach the cardiac, pulmonary, and esophageal plexus (consisting of both sympathetic and parasympathetic axons). From the esophageal plexus, right and left gastric nerves arise to supply the abdominal viscera as far caudal as the splenic flexure.

In the body, the vagus nerve regulates viscera, swallowing, speech, and taste. It has sensory, motor, and parasympathetic components. Table two below outlines the innervation and function of these components.

Table 2 - Vagus Nerve Components

Component fibers	Structures innervated	Functions
SENSORY	Pharynx, larynx, esophagus, external ear	General sensation
	Aortic bodies, aortic arch	Chemo- and baroreception
	Thoracic and abdominal viscera	
MOTOR	Soft palate, pharynx, larynx, upper esophagus	Speech, swallowing
PARASYMPATHETIC	Thoracic and abdominal viscera	Control of cardiovascular system, respiratory and gastrointestinal tracts

On the afferent side, visceral sensation is carried in the visceral sensory component of the vagus nerve. As shown in FIG. 19, visceral sensory fibers from plexus around the abdominal viscera converge and join with the right and left gastric nerves of the vagus. These nerves pass upward through the esophageal hiatus (opening) of the diaphragm to merge with the plexus of nerves around the esophagus. Sensory fibers from plexus around the heart and lungs also converge with the esophageal plexus and continue up through the thorax in the right and left vagus nerves. As shown in FIG. 20, the central process of the nerve cell bodies in the inferior vagal ganglion enter the medulla and descend in the tractus solitarius to enter the caudal part of the nucleus of the tractus solitarius. From the nucleus, bilateral connections important in the reflex control of cardiovascular, respiratory, and gastrointestinal functions are made with several areas of the reticular formation and the hypothalamus.

In summery, the afferent fibers project primarily to the nucleus of the solitary tract, shown schematically in FIG. 21, which extends throughout the length of the

medulla oblongata. A small number of fibers pass directly to the spinal trigeminal nucleus and the reticular formation. As shown in FIGS. 21 and 22, the nucleus of the solitary tract has widespread projections to cerebral cortex, basal forebrain, thalamus, hypothalamus, amygdala, hippocampus, dorsal raphe, and cerebellum. Because of the widespread projections of the Nucleus of the Solitary Tract, neuromodulation of the vagal afferent nerve fibers produce alleviation of symptoms of neurological disorders such as epilepsy, involuntary movement disorders and the like, and neuropsychiatric disorders such as depression, anxiety disorders and the like which are also covered in this patent application.

This application is related to two pending applications listed below, both applications filed on 05/11/03, entitled:

1. Application serial no. 10/436017, entitled - METHOD AND SYSTEM OF PROVIDING PULSED ELECTRICAL STIMULATION TO A CRANIAL NERVE OF A PATIENT TO PROVIDE THERAPY FOR NEUROLOGICAL AND NEUROPSYCHIATRIC DISORDERS; and
2. Application serial no. 10/436006, entitled - METHOD AND SYSTEM FOR PROVIDING PULSED ELECTRICAL STIMULATION TO SACRAL PLEXUS OF A PATIENT TO PROVIDE THERAPY FOR URINARY INCONTINENCE AND UROLOGICAL DISORDERS.

SUMMARY OF THE INVENTION

The current invention discloses a system and method for providing electrical pulses to one or both (left and right) vagus nerve(s) (and branches) of a patient, with an implantable stimulator. The implantable stimulator comprising a battery operated pulse generator module, and a stimulus-receiver module for coupling with an external stimulator, and controlling means to selectively control the operations of pulse generator module and a stimulus-receiver module. The invention provides selective stimulation or neuromodulation to one or both vagus nerve(s) to provide therapy for obesity, eating disorders, neurological and neuropsychiatric disorders.

One object of the present invention is to provide an improved system and method for pulsed electrical stimulation to provide therapy for obesity, eating disorders, neurological disorders and neuropsychiatric disorders. Another object is to derive at the optimal pulsed electrical stimulation dose for the individual patient

conveniently, where an attending physician can activate (or de-activate) the therapy programs from a remote location. A further object is to extend the service life of the implanted stimulator, whereby more intensive therapy can be given if appropriate, and surgical interventions to replace implanted stimulators can be minimized.

Accordingly in one aspect of the invention, the system comprises an implantable stimulator along with one or two implantable leads, an external stimulator, and a programmer. The implantable stimulator comprising a pulse generator module deriving power from an implanted battery, and a stimulus-receiver module deriving power from an external stimulator. Control circuitry means ensures selective operation of one of the pulse generator module or stimulus-receiver module. The implanted pulse generator module delivering electric stimulation therapy to vagus nerve(s) according to pre-determined parameters programmed by the programmer. The implanted stimulator system operates according to one of a programs stored in the memory. Upon receiving stimulus energy from an inductively coupled external stimulator, the implanted pulse generator module goes into "sleep" mode. The length of time that the implanted battery operated pulse generator module stays in "sleep" mode is a programmable parameter.

In one aspect of the invention, the pulsed electrical stimulation to vagus nerve(s) may be unilateral or bilateral. Bilateral stimulation may be provided by two leads and one stimulator.

In one aspect of the invention, bilateral stimulation may be provided by two independent implanted stimulators.

In another aspect of the invention, the site of stimulation may be at any level along the length of the vagus nerve(s). The site of electrode placement, and stimulation being around the diaphragmatic level, and may be slightly above the diaphragm, or slightly below the diaphragm.

In another aspect of the invention, the external stimulator is adapted to be remotely controllable via the internet. The external stimulator comprises a number of predetermined programs comprising unique combinations of variables of current output, pulse width, pulse frequency, and on-off timing sequence. Several of these programs are locked out to the patient, and can be activated (or de-activated) remotely via the internet, by the medical staff or physician. Since each patient is unique, different stimulation parameters can be tried by the patient, without the

patient having to travel to the clinic for programming. Once the optimal stimulation therapy program is identified, the patient can have the implanted stimulator programmed to the optimal settings.

In another aspect of the invention, the external stimulator may be used in conjunction with the implanted stimulus-receiver in order to extend the service life of the implantable stimulator or to temporarily deliver higher stimulation, or more aggressive therapy for specific situations.

In another aspect of the invention, with some modification in the circuitry, the implantable stimulator may be used as a re-chargeable implantable pulse generator to provide therapy for neurological, neuropsychiatric, and obesity and eating disorders applications.

In another aspect of the invention, the stimulator system comprises a telemetry module and is adapted to be networked for bi-directional communications wherein such communications capabilities can be used for at least one of patient monitoring and management, patient billing and invoicing, and patient location tracking using global position system (GPS).

In another aspect of the invention the implantable stimulator may be programmerless, whereby limited programmability can be realized with a magnet.

BRIEF DESCRIPTION OF THE DRAWINGS

For the purpose of illustrating the invention, there are shown in accompanying drawing forms which are presently preferred, it being understood that the invention is not intended to be limited to the precise arrangement and instrumentalities shown.

FIG. 1 is a schematic drawing showing innervation of the left vagus nerve to the stomach area.

FIG. 2 is a schematic drawing showing detailed innervation of the left vagus nerve to the thoracic and viceral organs.

FIG. 3 is a schematic diagram showing the relationship of meals and satiety signals.

FIG. 4 is a schematic diagram showing impulses traveling via the vagus nerve in response to gastric distention and CCK release.

FIG. 5A is a diagram showing bilateral vagus nerve stimulation.

FIG. 5B is a diagram showing sub-diaphramatic bilateral vagus nerve stimulation, using two implanted stimulators.

FIG. 5C is a diagram showing supra-diaphramatic bilateral vagus nerve stimulation using two implanted stimulators.

FIG. 5D is a diagram showing unilateral stimulation.

FIG. 5E is a diagram showing gastric stimulation.

FIG. 6 diagrammatically illustrates the concept of an implantable pulse generator (IPG) being used as a stand alone pulse generator, or used as a stimulus-receiver in conjunction with an external stimulator 42.

FIG. 7 is a diagram showing the two modules of the IPG.

FIG. 8 shows schematic of a physician remotely controlling the stimulation device via the internet.

FIG. 9A is a diagram showing internet communication of the external stimulator, via a portable PC.

FIG. 9B is a diagram showing communication of the external stimulator with the internet.

FIG. 10 is a diagram showing a physician communicating with a remote external stimulator from a hand-held device through a server.

FIG. 11 is a diagram of the structure of a nerve.

FIG. 12 is a table showing different types of nerve fibers, and their properties.

FIGS. 13A, 13B, 13C are schematic illustrations of the electrical properties of nerve cell membrane.

FIG. 14 is a diagram showing recordings of compound action potentials.

FIG. 15 is a schematic illustration, showing painful stimulation being carried to brain via large diameter and small diameter fibers.

FIG. 16 is a schematic illustration, showing mild stimulation being carried to brain, via large diameter and small diameter fibers.

FIG. 17 is a schematic illustration showing afferent 19 and efferent 21 transmission.

FIG. 18 is a schematic diagram showing the vagus nerve at the level of the nucleus of the solitary tract in the brain stem.

FIG. 19 is a schematic diagram showing the thoracic and visceral innervations of the vagal nerves.

FIG. 20 is a schematic diagram of the medullary section of the brain, showing ganglion of vagus nerve.

FIG. 21 is a simplified block diagram illustrating the connections of solitary tract nucleus to other centers of the brain.

FIG. 22 is a simplified schematic diagram of brain showing the relationship of the solitary tract nucleus to other centers of the brain.

FIG. 23 is a schematic and functional block diagram showing the components and their relationships to the implantable pulse generator/stimulus-receiver.

FIG. 24 shows details of implanted pulse generator.

FIG. 25 shows details of digital components of the implantable circuitry.

FIGS. 26A, 26B and 26C show output pulses from a comparator when input exceeds a reference voltage.

FIGS. 27A and 27B show assembly features of the implantable portion of the system.

FIGS. 28A and 28B are simplified block diagrams showing the switching relationships between the inductively coupled and battery powered assemblies of the pulse generator.

FIG. 29 is a diagram depicting the closure of a magnetic (Reed) switch with a magnet.

FIGS. 30A and 30B are diagrams showing communication of programmer with the implanted stimulator 75.

FIGS. 31A and 31B show diagrammatically encoding and decoding of programming pulses.

FIG. 32 diagrammatically shows secure communication for programming pulses in a simplified manner.

FIG. 33 is a block diagram for generation of a pre-determined stimulation pulse.

FIG. 34 is a simplified schematic for delivering stimulation pulses.

FIG. 35 is a diagram depicting ramping-up of a pulse train.

FIG. 36 is a diagram of an implantable lead with electrodes for stimulation.

FIG. 37A is diagram depicting stimulating electrode-tissue interface.

FIG. 37B is diagram depicting an electrical model of the electrode-tissue interface.

FIG. 38 is a functional block diagram of the external stimulator.

FIG. 39 is a simplified block diagram of the networking interface board.

FIG. 40 is a diagram showing physician communication over the internet, with a modified PDA/phone

FIG. 41 is a diagram showing physician's communication for billing over the internet with a modified PDA/phone

FIGS. 42A and 42B is a simplified diagram showing communication of modified PDA/phone with an external stimulator via a cellular tower/base station.

FIG. 43 depicts the migration paths to 3G ("third generation") technologies.

FIG. 44 depicts wireless communication of an external stimulator via an access point router (AP).

FIGS. 45A and 45B show a physician communicating and exchanging data with a modified PDA/phone using wireless access point.

FIG. 46 is a flow diagram for physician initiated nerve stimulation therapy review.

FIG. 47 is a flow diagram for billing procedure over the internet using a modified PDA/phone.

FIG. 48 is a flow diagram for patient initiated nerve stimulation therapy review.

FIG. 49 is a simplified block diagram of the location tracking interface board.

FIG. 50 depicts an embodiment where the implantable system is used as an implantable, rechargeable system.

FIG. 51 is a diagram depicting different varieties of the system of the invention.

FIG. 52 is a schematic and block diagram depicting a simpler version of the implantable pulse generator.

FIG. 53 is a schematic diagram depicting digital circuitry for state machine.

DETAILED DESCRIPTION OF THE INVENTION

The following description is of the current embodiment for carrying out the invention. This description is not to be taken in a limiting sense, but is made merely for the purpose of describing the general principles of the invention.

As shown in FIG. 6, the system of the present invention comprises, an implanted stimulator 75, implanted lead 40, an external stimulator 42, and an external programmer 85. As shown in FIG. 7, the implantable stimulator 75 contains two stimulator assemblies 68,70 which operate in a coordinated fashion with control circuitry coordinating the two assemblies. The stimulus-receiver module 68, which is outside of the titanium can 65 is similar to an inductively coupled stimulation system, known in the art as "RF Neurostimulation System". The second assembly, which is encased in a titanium can 65 is the implanted pulse generator (IPG) 70 deriving power from an implanted battery. Control circuitry means ensures that the two assemblies operate correctly, and in a coordinated fashion.

A simplified schematic and block diagram of the implantable stimulator 75 is shown in FIG. 23. The inductively coupled stimulus-receiver module 68 is shown in the left part of the diagram, and the battery-operated portion 70 is shown on right side of the diagram. The battery-operated portion 70 is also referred to as IPG 70, implanted pulse generator 70, stimulator subassembly 70, and battery operated module 70 in this disclosure. Much of the circuitry included within this embodiment of the IPG 70 is realized on single application specific integrated circuit (ASIC). This allows the overall size of the IPG 70, to be quite small and readily housed within a suitable hermetically-sealed case, such as one made of titanium. Using CMOS technology and monolithic design, the analog and digital functions are integrated on a silicon chip approximately 5 mm x 5 mm in size. Hybrid technology being used as a reliable connection technology for the wiring of the IC with non-integrated discrete components (like quartz oscillators, tantalum capacitors, coils of transmission, reed contacts, etc).

The implantable stimulator 75 is implanted in a patient, in the usual fashion by making an incision to expose the nerve(s) for placement of the electrode approximately just above or below the level of the diaphragm. One pair of electrodes is placed for unilateral stimulation or two pairs of electrodes are placed (using 2 leads) for bilateral stimulation. The single lead 40 or both leads are connected to the pulse generator 75. The pulse generator 75 is placed in a bluntly dissected pocket. The incision is closed in layers in the usual manner, and stimulation can begin after the tissues are healed (approximately 2 weeks).

Once implanted, in the system and method of this invention, pulsed electrical stimulation can be performed either via an external stimulator 42 in conjunction with the stimulus-receiver module 68 (FIG. 6), or via the implanted pulse generator 70 according to parameters which are programmed via an external programmer 85. It also being understood that there may be two stimulators and two separate leads as shown in FIGS. 5B and 5C.

In one aspect of the invention, the physician can asses the stimulation parameters in terms of efficacy and tolerability to the patient, by using the external stimulator 42 in conjunction with the stimulus-receiver module 68. Advantageously, the external stimulator 42 is networked, and can be controlled by a physician via the internet, from a distant location. Once the optimal stimulation parameters are assessed and the stimulation dose is "titrated", the stimulation parameters can then be programmed into the implanted pulse generator 70 using the external programmer 85.

The "tuning" of the vagus nerve 54 (or another cranial nerve), for a particular patient, can be performed in one of two ways with the external stimulator 42. One method is to activate one of several "pre-determined" programs. A second method is to "custom" program the electrical parameters which can be selectively programmed, for specific disease state of the individual patient. Selected useful "customized" programs can then be saved in the memory of the external stimulator 42. The electrical parameters that can be individually programmed, include variables such as pulse amplitude, pulse width, pulses per second, stimulation on-time, and stimulation off-time among others.

The system of the present invention is designed such that when stimulation is applied via the external stimulator 42 through the primary (external) coil 46, and is picked up by the implanted (secondary) coil 48, the battery operated stimulation module (IPG) 70 is temporarily suspended. This is accomplished through the comparator circuitry 178, 180 which sends a control signal to the controller 184, causing the battery operated stimulator module 70 to suspend operation and go into "sleep mode". The length of time for this "sleep mode" is programmable with the external programmer 85.

The external stimulator 42 comprises numerous pre-packaged programs, which may range anywhere from two to three hundred programs. In addition,

"customized" programs specifically tailored to the physiology of the individual patient, can be generated and stored in one of the several memories available in the external stimulator 42. New programs can be loaded into the external stimulator 42, preferably as described in U.S. Patent No. 6,366,814 B1, incorporated herein by reference. Each pre-packaged program comprises a unique combination of electrical pulse stimulation parameters such as pulse amplitude, pulse width, number of pulses per second, on-time and off-time. Examples of mild stimulation programs may be,

Program #1:

0.75 mA current output, 0.2 msec pulse width, 15 Hz frequency, 15 sec ON time-1.0 min OFF time, in repeating cycles.

Program #2:

1.0 mA current output, 0.3 msec pulse width, 20 Hz frequency, 20 sec ON time-2.0 min OFF time, in repeating cycles.

The following are examples of intermediate level of therapy.

Program #5:

2.0 mA current output, 0.2 msec pulse width, 25 Hz frequency, 20 sec ON time-1.0 min OFF time, in repeating cycles.

Program #6:

2.5 mA current output, 0.25 msec pulse width, 25 Hz frequency, 30 sec ON time-1.0 min OFF time, in repeating cycles.

The following are examples of more aggressive therapy.

Program #8:

2.5 mA current output, 0.3 msec pulse width, 30 Hz frequency, 40 sec ON time-1.5 min OFF time, in repeating cycles.

Program #9:

3.0 mA current output, 0.4 msec pulse width, 40 Hz frequency, 30 sec ON time-1.0 min OFF time, in repeating cycles.

It being understood, that the above programs are examples only, and the actual programs may deviate from these programs.

In addition to the prepackaged programs, customized stimulation programs may be programmed from a range of parameters shown in Table 3.

Table 3--Electrical parameter range delivered to the nerve

PARAMER	RANGE
Pulse Amplitude	0.1 Volt - 10 Volts
Pulse width	20 μS - 5 mSec.
Frequency of pulses	5 Hz - 200 Hz
On-time	3 Secs - 24 hours
Off-time	10 Secs - 24 hours

The parameters in Table 3 are the electrical signals delivered to the nerve via the two electrodes 61,62 (distal and proximal) around the nerve, as shown in FIG. 5A. It being understood that the signals generated by the external stimulator and transmitted via the primary coil 46 (antenna) are larger, because the attenuation factor between the primary coil 46 and secondary coil 48 is approximately 10-20 times, depending upon the distance, and orientation between the two coils 46, 48. Accordingly, the range of transmitted signals of the external pulse generator 42 are approximately 10-20 times larger than shown in Table 3.

In the method and system of current invention, much of the stimulation parameter "dose" titration, and patient tolerability to "aggressive" stimulation can be performed without the patient having to go to the clinic or physician's office for programming. Many of the pre-packaged programs may be initially locked out to the

patient. During the course of therapy, the physician can selectively activate the few programs that the patient is going to try for evaluating efficacy of therapy and patient tolerance. The remote activation and de-activation of selected pre-packaged programs may be performed by the Physician or medical staff from a distant location using cable modem and internet, preferably as described in a co-pending application serial # 09/794530. Alternatively, the medical staff can activate (and de-activate) selected pre-packaged programs over the wireless internet as disclosed in another co-pending application serial # 09/837565. Both of the disclosures being incorporated herein in their entirety by reference. Such activation and de-activation of selected pre-packaged programs may be used in "titrating" the optimal dose for therapy.

Patient tolerance to such nerve stimulation therapy can vary widely. Once the particular patient's tolerance and response is "characterized", the stimulation parameters can be programmed into the battery operated module 70 of the implanted stimulator 75 via an external programmer 85.

With reference to FIG. 23, for the functioning of the inductively coupled stimulus-receiver 68, a primary (external) coil 46 is placed in close proximity to secondary (implanted) coil 48. The primary coil 46 may be taped to skin 90, or other means may be used for keeping the primary coil in close proximity. Referring to the left portion of FIG. 23, the amplitude and pulse width modulated radiofrequency signals from the primary (external) coil 46 are electromagnetically coupled to the secondary (implanted) coil 48 in the implanted unit 75. The two coils, 46 and 48 thus act like an air-gap transformer. The system having means for proximity sensing between the two coils and feedback regulation of signals as described more fully in U.S. Patent No. 6,473,652 B1, which is incorporated herein in its entirety by reference.

Again with reference to FIG. 23, the combination of capacitor 152 and inductor 48 tunes the receiver circuitry to the high frequency of the transmitter with the capacitor 152. The receiver is made sensitive to frequencies near the resonant frequency of the tuned circuit and less sensitive to frequencies away from the resonant frequency. A diode bridge 154 rectifies the alternating voltages. Capacitor 158 and resistor 164 filter out the high-frequency component of the receiver signal, and leaves the current pulse of the same duration as the bursts of the high-

frequency signal. A zenor diode 169 is used for regulation and capacitor 166 blocks any net direct current.

As shown in conjunction with FIG. 26A the pulses generated from the stimulus receive circuitry 68 are compared to a reference voltage, which is programmed in the implanted pulse generator 70. When the voltage of incoming pulses exceeds the reference voltage (FIG. 26B), the output of the comparator 178,180 sends digital pulse 89 (shown in FIG. 26C) to the stimulation electric module 184. At this predetermined level, the high threshold comparator 178 fires and the controller 184 suspends any stimulation from the implanted pulse generator 70. The implanted pulse generator 70 goes into "sleep" mode for a predetermined period of time. In the presently preferred embodiment, the level of voltage needed for the battery operated stimulator to go into "sleep" mode is a programmable parameter. The length of time, the implanted pulse generator 70 remains in "sleep" mode is also a programmable parameter. Therefore, advantageously the external stimulator 42 in conjunction with the inductively coupled part of the stimulator 68 can be used as much as needed by the patient, and prescribed by the physician.

In the preferred embodiment, the external stimulator 42 is networked using the internet, giving the attending physician full control for activating and de-activating selected programs. Using "trial and error" various programs for electrical pulse therapy can be custom adjusted for the physiology of the individual patent. Also, by using the external stimulator 42, the battery 188 of the implanted stimulator unit 75 can be greatly extended. Further, even after the battery 188 is depleted, the system can still be used for neuromodulation using the stimulus-receiver module 68, and the external stimulator 42.

At some point, the implanted pulse generator 70 is programmed with the external programmer 85, using a modified PC and a programming wand 87, as is shown in FIGS. 30A and 30B.

The battery-operated portion of the system 70 is shown on the right side of FIG. 23 and is described in conjunction with FIGS. 24 and 25. The stimulation electronic module 184 comprises both digital and analog circuits. The main timing generator 330 (shown in FIG. 24), controls the timing of the analog output circuitry for delivering neuromodulating pulses to the vagus nerve 54, via output amplifier 334. Limiter 183 prevents excessive stimulation energy from getting into the vagus

nerve. The main timing generator 330 receiving clock pulses from crystal oscillator 186. Main timing generator 330 also receiving input from inductively coupled circuitry 68, and programmer 85 via coil 172. FIG. 25 highlights other portions of the digital system such as CPU 338, ROM 337, RAM 339, program interface 346, interrogation interface 348, timers 340, and digital O/I 342.

Most of the digital functional circuitry 350 is on a single chip (IC). This monolithic chip along with other IC's and components such as capacitors and the input protection diodes are assembled together on a hybrid circuit. As well known in the art, hybrid technology is used to establish the connections between the circuit and the other passive components. The integrated circuit is hermetically encapsulated in a chip carrier. A coil situated under the hybrid substrate is used for bidirectional telemetry. For the implanted battery portion 70, the hybrid and battery 188 are encased in a titanium can 65. This housing is a two-part titanium capsule that is hermetically sealed by laser welding. Alternatively electron-beam welding can also be used. The header 79 (FIG. 7) is a cast epoxy-resin with hermetically sealed feedthrough, and form the lead 40 connection block. The stimulus-receiver assembly 68 is then also assembled on to the pulse generator 70 to finish the complete implanted stimulator 75.

FIG. 27A shows a picture of the finished implantable stimulator 75. FIG. 27B shows the pulse generator with some of the components used in assembly in an exploded view. These components include a coil cover 7, the secondary coil 48 and associated components, a magnetic shield 9, and a coil assembly carrier 11. The coil assembly carrier 11 has at least one positioning detail 80 located between the coil assembly and the feed through for positioning the electrical connection. The positioning detail 80 secures the electrical connection.

FIG. 28A is a simplified diagram of one aspect of control circuitry. In this embodiment, to program the implanted portion of the stimulator 70, a magnet 144 is placed over the implanted pulse generator 70, causing a magnetically controlled Reed Switch 182 (which is normally in the open position) to be closed (shown in FIG. 29). As is also shown in FIG. 28A, at the same time a switch 67 going to the stimulator lead 40, and a switch 69 going to the circuit of the stimulus-receiver module 68 are both opened, completely disconnecting both subassemblies electrically. Further, protection circuitry 181 is an additional safeguard for

inadvertent leakage of electrical energy into the nerve tissue 54 during programming. Alternatively, as shown in FIG. 28B, instead of a reed switch 182, a solid state magnet sensor (Hall-effect sensor) 146 may be used for the same purpose. In the presently preferred embodiment, the solid state magnet sensor 146 is preferred, since there are no moving parts that can get stuck.

With the magnet sensor switch 146 (or Reed Switch 182) in the closed position, a coil 192 in the head of the programmer, communicates with a telemetry coil 172 (shown in FIG. 23) of the implanted pulse generator 70. Bidirectional inductive telemetry is used to exchange data with the implanted unit 70 by means of the external programming unit 85. As shown in conjunction with FIGS. 30A, 30B, 31A and 31B, inductive coupling is also employed to transmit the programming instructions, which are detected by a receiving element, which is the antenna coil 172. These pulses of the magnetic field are transmitted in a coding scheme that induces current to flow in the antenna coil 172. Programming takes place via coil 172, a receiving amplifier, a decoder, a controller, and the register in which the temporary and permanent programs are stored. Radiofrequency (RF) waves of electromagnetic field using frequencies of approximately 100 KHz, that allow rapid transmission of large amounts of information. Both the transmitter (in the programmer 85) and the receiver (in the pulse generator 172) have antennae (coils) for emitting and decoding RF signals. The RF frequency is modulated, allowing the encoding of information during transmission by the programmer 85. The receiver coil 172 is tuned through properly selected inductor-capacitor values to have unique sensitivity to the carrier frequency of the transmitted signals.

The transmission of programming information involves manipulation of the carrier signal in a manner that is recognizable by the pulse generator 70 as a valid set of instructions (shown in conjunction with FIGS. 30A and 30B). The process of modulation serves as a means of encoding the programming instruction in a language that is interpretable by the pulse generator. Modulation of signal amplitude, pulse width, and time between pulses are all used in the programming system, as will be appreciated by those skilled in the art. FIG. 31A shows an example of pulse count modulation, and FIG. 32B shows an example of pulse width modulation.

The programming signal of the current system is designed to be secure. Several schemes can be used, as will be appreciated by those skilled in the art. For example, using the first group of bits and pulses as an identification or access code. Another example of programming signal security is shown in FIG. 32. An x number of pulses are organized into pairs to send a code message of x/2 digital bits that allow different levels of " safety interlocks".

Once the implanted pulse generator 70 is programmed, it operates continuously until a signal is received from the stimulus-receiver module 68, via the high threshold comparator 178. As shown in FIG. 23, the controller 184 of the IPG 70 controls the output amplifiers. The pulses have predetermined energy (pulse amplitude and pulse width) and are delivered at a time determined by the therapy stimulus controller. The circuitry in the output amplifier, shown in conjunction with (FIG. 33) generates an analog voltage or current that represents the pulse amplitude. The stimulation controller module 184 initiates a stimulus pulse by closing a switch 208 that transmits the analog voltage or current pulse to the nerve tissue through the tip electrode 61 of the lead 40. The output circuit receiving instructions from the stimulus therapy controller 184 that regulates the timing of stimulus pulses and the amplitude and duration (pulse width) of the stimulus. The pulse amplitude generator 206 determines the configuration of charging and output capacitors necessary to generate the programmed stimulus amplitude. The output switch 208 is closed for a period of time that is controlled by the pulse width generator 204. When the output switch 208 is closed, a stimulus is delivered to the tip electrode 61 of the lead 40.

The constant-voltage output amplifier applies a voltage pulse to the distal electrode (cathode) 61 of the lead 40. A typical circuit diagram of a voltage output circuit is shown in FIG. 34. This configuration contains a stimulus amplitude generator 206 for generating an analog voltage. The analog voltage represents the stimulus amplitude and is stored on a holding capacitor C_h 225. Two switches are used to deliver the stimulus pulses to the lead 40, a stimulating delivery switch 220, and a recharge switch 222, that reestablishes the charge equilibrium after the stimulating pulse has been delivered to the nerve tissue. Since these switches have leakage currents that can cause direct current (DC) to flow into the lead system 40, a DC blocking capacitor C_b 229, is included. This is to prevent any possible corrosion

that may result from the leakage of current in the lead 40. When the stimulus delivery switch 220 is closed, the pulse amplitude analog voltage stored in the (C_h 225) holding capacitor is transferred to the cathode electrode 61 of the lead 40 through the coupling capacitor, C_b 229. At the end of the stimulus pulse, the stimulus delivery switch 220 opens. The pulse duration being the interval from the closing of the switch 220 to its reopening. During the stimulus delivery, some of the charge stored on C_h 225 has been transferred to C_b 229, and some has been delivered to the lead system 40 to stimulate the nerve tissue.

To re-establish equilibrium, the recharge switch 222 is closed, and a rapid recharge pulse is delivered. This is intended to remove any residual charge remaining on the coupling capacitor C_b 229, and the stimulus electrodes on the lead (polarization). Thus, the stimulus is delivered as the result of closing and opening of the stimulus delivery 220 switch and the closing and opening of the RCHG switch 222. At this point, the charge on the holding C_h 225 must be replenished by the stimulus amplitude generator 206 before another stimulus pulse can be delivered.

Referring back to FIG. 23, for the implanted power source, lithium iodine is preferred in the current embodiment, because of its long history in cardiac pacemakers. However, other power sources where lithium is combined with other cathode materials may be used, such as lithium cooper sulfide, lithium silver vanadium pentoxide, lithium bromine chloride, or lithium sulfuryl chloride cell.

FIG. 35 shows an example of the pulse trains that are delivered. The microcontroller is configured to deliver the pulse train as shown in the figure, i.e. there is "ramping up" of the pulse train. The purpose of the ramping-up is to avoid sudden changes in stimulation, when the pulse train begins.

Moving now to FIG. 36, the implanted lead 40 component of the system is similar to cardiac pacemaker leads, except for distal portion of the lead (or the electrode end of the lead). In the presently preferred embodiment, the lead terminal is a linear bipolar (though a bifurcated terminal can also be used), and plug(s) into the header 79 of the pulse generator 75 (shown in FIG. 7). The lead body insulation 59 may be constructed of polyurethane, medical grade silicone, or silicone reinforced with polytetrafluoro-ethylene (PTFE). The electrodes 61,62 for stimulating the vagus nerve(s) 54 may either wrap around the nerve once or may be spiral shaped. These stimulating electrodes may be made of pure platinum, platinum/Iridium alloy or

platinum/iridium coated with titanium nitride, and are described more fully in U.S. patent 6,205,359 which is incorporated here by reference. The conductor connecting the terminal to the electrodes is made of an alloy of nickel-cobalt.

The choices for implanted lead design variables are also summarized in the table below.

Table of lead design variables

Proximal End — Distal End

Lead Terminal	Lead body-Insulation Materials	Lead-Coating	Conductor (connecting proximal and distal ends)	Electrode - Material	Electrode - Type
Linear Bipolar	Polyurethane	Antimicrobial coating	Alloy of Nickel-Cobalt	Pure Platinum	Spiral electrode
Bifurcated	Silicone	Anti-Inflamatory coating		Platinum-Iridium (Pt/IR) Alloy	Wrap-around electrode
	Silicone with Polytetrafluoro-ethylene (PTFE)	Lubricious coating		Pt/Ir coated with Titanium Nitride	Steroid eluting
				Carbon	

Once the lead 40 is fabricated, coating such as anti-microbial, anti-inflammatory, or lubricious coating may be applied to the body of the lead 59.

FIG. 37A summarizes electrode-tissue interface between the nerve tissue and electrodes 61, 62. There is a thin layer of fibrotic tissue between the stimulating electrode 61 and the excitable nerve fibers of the vagus nerve 54. FIG. 37B

summarizes the most important properties of the metal/tissue phase boundary in an equivalent circuit diagram. Both the membrane of the nerve fibers and the electrode surface are represented by parallel capacitance and resistance. Application of a constant battery voltage V_{bat} from the pulse generator 75, produces voltage changes and current flow, the time course of which is crucially determined by the capacitive components in the equivalent circuit diagram. During the pulse, the capacitors C_o, C_h and C_m are charged through the ohmic resistances, and when the voltage V_{bat} is turned off, the capacitors discharge with current flow on the opposite direction.

Moving now to the external pulse generator 42, which is shown in conjunction with FIG. 38. The external pulse generator 42 is composed of various modules or sub-assemblies. The first sub-assembly is the pulse generation and signal conditioning components 113,114, the second is the battery 116, and the third is the telemetry 121 and memory unit 123. The presently preferred embodiment, comprises proximity sensing and feedback circuitry, even though the pulse generator is able to function as supplier of electric pulses to the nerve tissue 54 without the proximity feedback loop. These modules or sub-assemblies also provide for a scalable external pulse generator 42. In the telemetry module, a wireless antenna 129 provides a means for communication to the external pulse generator 42 and the wireless remote server 189. In one embodiment, a programming unit 119 can be physically connected to the stimulator 42 (via the Programming Unit Interface 120) in a tethered manner for loading of new predetermined programs or changing parameters of an existing program.

Also shown in conjunction with FIG. 38, the pre-packaged programs are stored in the memory unit 123. This represents memory with a readable and writeable portion and a non-volatile pre-programmable portion. A Field Programmable Array Unit (FPGA) 111 and a random access component (RAM) and Random addressable storage logic, facilitates the application of logic to edit and change the "current" parameters being utilized for pulse generation. The programmable unit interface 120 provides an interface to a programming unit (portable computer system) 119, which allows re-loading of a new set of predetermined programs. The pulse generation component 113 generates pulses of well-defined parameters, selected from the programmed parameters that exist in the memory unit 123. The pulse signal generation unit 113 provides its signal to be

amplified and conditioned at the amplifier and signal conditioning unit 114 which then provides these signals to the primary (external) inductive coil 46. In one embodiment, the sensor unit 126 has a pair of sensors which sense the position of the implanted magnet 127, and the sensor signal is fed back to the proximity sensor control block 110 via the feedback signal conditioning unit 112. The feedback signal provides a proportional signal for modification of the frequency, amplitude and pulse-width of the pulse being generated by the pulse signal generator unit 113. The sensor unit 126 has two sensors 124, 125 that sense the location of the implanted magnet 127. In one embodiment, the implanted (secondary) coil 48 is rigidly connected to the passive circuit and magnet 127. The skin 90 separates the subcutaneous and external components. The external components are placed on the skin 90, with the primary coil 46 in close proximity and optimally situated with respect to the implanted (secondary) coil 48.

As explained before, the implanted unit 75 communicates with the external stimulator 42 via inductive coupling between primary 46 and secondary coil 48. In one aspect of the invention, as shown in FIG. 39, the external stimulator 42, and the programmer 85 are capable of being networked 290 to a central collaboration computer 286 as well as other devices such as a remote computer 294, PDA 140, phone 141, physician computer 143. This minimizes situations in which the physical transport of a patient to a particular clinical setting is required.

The interface unit 292 in the preferred embodiment communicates with the central collaborative network 290 via land-lines such as cable modem or wirelessly via the internet. A central computer 286 which has sufficient computing power and storage capability to collect and process large amounts of data, contains information regarding device history and serial number, and is in communication with the network 290. Communication over collaboration network 290 may be effected by way of a TCP/IP connection, particularly one using the internet, as well as a PSTN, DSL, cable modem, LAN, WAN or a direct dial-up connection.

The standard components of interface unit shown in block 292 are processor 305, storage 310, memory 308, transmitter/receiver 306, and a communication device such as network interface card or modem 312. In the preferred embodiment these components are embedded in the external stimulator 42 and can also be

embedded in the programmer 85. These can be connected to the network 290 through appropriate security measures (Firewall) 293.

Another type of remote unit that may be accessed via central collaborative network 290 is remote computer 294. This remote computer 294 may be used by an appropriate attending physician to instruct or interact with interface unit 292, for example, instructing interface unit 292 to send instruction downloaded from central computer 286 to remote implanted unit 75.

Taking advantage of this networking, as shown in conjunction with FIGS. 40 and 41, in one embodiment of the invention, as the physician interrogates the device, reviews the patient history, and programs the device, an invoice is generated in the physician's office computer.

Shown in conjunction with FIGS. 42A and 42B the physician's remote communication's module is a Modified PDA/Phone 140 in this embodiment. The Modified PDA/Phone 140 is a microprocessor based device as shown in a simplified block diagram in FIGS 42A and 42B. The PDA/Phone 140 is configured to accept PCM/CIA cards specially configured to fulfill the role of communication module 292 of the present invention. The Modified PDA/Phone 140 may operate under any of the useful software including Microsoft Window's based, Linux, Palm OS, Java OS, SYMBIAN, or the like.

The telemetry module 362 comprises an RF telemetry antenna 142 coupled to a telemetry transceiver and antenna driver circuit board which includes a telemetry transmitter and telemetry receiver. The telemetry transmitter and receiver are coupled to control circuitry and registers, operated under the control of microprocessor 364. Similarly, within stimulator 42A and (FIG 42B) a telemetry antenna 142 is coupled to a telemetry transceiver comprising RF telemetry transmitter and receiver circuit. This circuit is coupled to control circuitry and registers operated under the control of microcomputer circuit.

With reference to the telecommunications aspects of the invention, the communication and data exchange between Modified PDA/Phone 140 and external stimulator 42 operates on commercially available frequency bands. The 2.4-to-2.4853 GHz bands or 5.15 and 5.825 GHz, are the two unlicensed areas of the spectrum, and set aside for industrial, scientific, and medical (ISM) uses. Most of the technology today including this invention, use either the 2.4 or 5 GHz radio

bands and spread-spectrum technology. The three types of spread-spectrum communication used in wireless networks are direct sequence spread spectrum (DSSS), frequency hopping spread spectrum (FHSS), and orthogonal frequency division multiplexing (OFDM). This invention contemplates using all three types of spread-spectrum communications, depending on the patient's circumstances. In an FHSS environment, signals hop among a series of subchannels in a random pattern understood by both transmitter and receiver. Each hop consists of short burst of data, and the amount of time between hops is referred to as dwell time. Although DSSS also spreads transmissions over multiple channels with a given frequency range, no hopping occurs between frequencies. Instead, a binary string called a spreading code creates redundant transmissions, increasing the chances that signals and data will reach the intended receiver intact. The sending wireless device must use the same spreading code as the sender for signals to pass between them. Restricting the devices to a particular code, rather than using several, reduces the interference potential on the channel used by the two devices. OFDM makes efficient use of available spectrum by dividing it into subchannels and sending a portion of a given data transmission over each one.

The telecommunications technology, especially the wireless internet technology, which this invention utilizes, is constantly improving and evolving at a rapid pace, due to advances in RF and chip technology as well as software development. Therefore, one of the intents of this invention is to utilize "state of the art" technology available for data communication between Modified PDA/Phone 140 and external stimulator 42. Shown in conjunction with FIG. 43 is the migration paths to what is commonly termed "3G" or third generation wireless internet. The intent of this invention is to use 3G technology for wireless communication and data exchange, even though in some cases 2.5G is being used currently.

In the United states, the CDMA technology that is available today (2.5G) will go through a series of CDMA upgrades. The 2.5G version is called cdma20001x while the 3G version is called cdma20003x. Each of these represents an increase or improvement in signal processing, bandwidth, and/or modulation. In Europe a path to 3G consists of several intermediate steps. The first of these intermediate steps (2.5G) is General Packet Radio Services or GPRS, which overlays packet switching on the existing GSM system. The next intermediate step is the Enhanced Data GSM

Environment or EDGE. Among other things, EDGE incorporates a modulation improvement to GPRS. From there the official "3G" system for Europe is Universal Mobile Telecommunications System or UMTS 486, which is a true packet switched network. In Japan, the first two generation pretty much worked in isolation with their 1G analog system (JTACS) 488 and their 2G digital system (PDC based on a TDMA air interface) 490. Because of all this uniformity, it was possible for Japan to essentially jump over 2.5G and go right to a 3G system. In Japan, which is the first country to deploy a system with 3G capabilities, the system is based on a WCDMA 492 air interface similar to that in UTMS 486.

For the system of the current invention, the use of any of the "3G" technologies for communication for the Modified PDA/Phone 140, is considered within the scope of the invention. Further, it will be evident to one of ordinary skill in the art, that as future 4G systems, which will include new technologies such as improved modulation and smart antennas, can be easily incorporated into the system and method of current invention, and are also considered within the scope of the invention.

As shown in conjunction with FIGS. 44, 45A, and 45B, one aspect of the invention takes advantage of wireless networking, specifically the WLAN connection as defined by the IEEE 802.11 standard. The WLANs currently operate on the 2.4 GHz and 5.2-5.8 GHz frequency bands. For example as shown in FIG. 44, a wireless Access Point (AP) may be set up in patient's home which already has a High Speed Data Connection, either via cable modem, high speed telephone line, or satellite based connection. When the patient is in his/her home, within the communication range of the AP Router 382, High Speed data communication via the internet occurs with the external stimulator 42. Typically the operating distances are in the order of 300 to 1,500 feet, but can be extended by the use of high-gain antennas and amplifiers to more than 10 miles. Since the WLAN connections are in the order of 11 to 54 Mbps or higher, the speed of data exchange will be limited by the speed of the internet connection.

Similarly, a physician using the Modified PDA/Phone 140 may gain access to the high speed wireless internet by being within the communication distance of an AP 382, whether in the office or any other place where an AP is available (FIG. 45A). FIG. 45B shows another configuration of a physician or physician group where a

Modified PDA/Phone 140 or other wireless computers gain access to high speed internet using an access pint 382.

The remote interrogation and programming of the stimulator 42 may be initiated at the request of the patient or may be initiated by the physician as shown in step 400 of FIG. 46. The physician's checking up on the patient and the device, may be a scheduled activity or be triggered by an event. The physician or medical personnel may look at the patient's history and external stimulator 42, device history either on the modified PDA 140 if available or by connecting to the office computer as shown in steps 402-410. Once the information is reviewed, the physician decides if the active stimulation parameters of the stimulator 42 need to be altered (step 412). If required, the changes are made and recorded in the office computer records. This information is also communicated to the patient, steps 414 and 416.

Further, as shown in conjunction with FIG. 47, the physician determines if billing for the session is required, step 418. In case billing is required, the Modified PDA/Phone 140 has stored in its memory, all the relevant billing codes and templates. Once the generated bill appears on the screen as shown in step 421, the physician reviews the bill for completeness, step 422. If the bill is complete, it may be e-mailed to payer as shown in step 432, or alternatively sent to main computer 436 for billing department to handle.

When a patient initiates request for therapy review as in step 440, shown in conjunction with FIG. 48, the physician or medical staff is contacted 442. The physician again looks to see if the patient information on the Modified PDA/Phone 140 is current, if not, then retrieves it from the server in physician's office 446. Then in a series of steps, similar to as described earlier, the physician reviews records, makes changes to the program if needed, contacts patient, and bills for the services if required, as shown in steps 444-458 and steps 418-436 (FIG. 47).

In one embodiment of the system, as shown in conjunction with FIG. 49, the programmer 85 also comprises global positioning system(GPS) receiver 241 for location tracking. Alternatively, the location tracking circuitry may be incorporated in the external stimulator 42. The system controller 307 contains a system lock for maintaining an accurate time base which may be re-calibrated periodically via accurate clocks in the GPS satellites 230. The microcomputer-based systems controller 307 is coupled to data communications network interface via data bus 238.

The system controller 307 may be part of a standard or modified cellular telephone or other personnel communication device.

At a medical support network 231, a base station is provided to be in the communication link with the patient-worn communication device. The base station is preferably a microprocessor-based system that includes the software and hardware needed for communication with the patients to locate the patient.

In accordance with one aspect of the invention, the system controller 307 is coupled to a GPS receiver 241 via bus 243 for receiving patient positioning data from an earth satellite 230. The GPS receiver 241 may use current systems such as the PCMCIA GPS Sensor. The GPS receiver 241 may be actuated by a command received through the system controller 307 from the medical support network 231 in the case of an emergency response.

Either or both PCMCIA cards 235 and 233 may be provided and they are coupled with the voice and communications network 234 via buses 236 and 237. When both are provided access to the communications satellite link 230 is automatically obtained when a link to a cellular transceiver 232 is not possible.

Based on the above disclosure, it will be clear to one of ordinary skill in the art, that with slight modification in the circuitry, other embodiments can be produced. For example, an implantable pulse generator with rechargeable power source. In such an embodiment (shown in conjunction with FIG. 50), the RF pulses transmitted via coil 46 and received via subcutaneous coil 48A are rectified via diode bridge 154. These DC pulses are processed and the resulting current applied to recharge the battery 188A in the implanted pulse generator.

As another example, it will also be obvious to one of ordinary skill in the art, that the current invention can be practiced with a cheaper and less programmable version of an implantable pulse generator. For example, as shown in FIG. 51 (bottom right), a programmer-less stimulator may be used, where a limited number of programs may be accessed via a magnet, preferably as disclosed in U.S. Patent No. 6,449,512 and incorporated here by reference.

As shown with reference to FIG. 52, in this version only a limited number of states are possible. For example LO, MED, MED-HI, HI stimulation states and an OFF state. Each state corresponds to a complete program comprising a unique combination of pulse amplitude, pulse width, pulses per second, ON-time and OFF-

time. By using just a magnet 92, each of these states can be programmed by swiping the magnet 92, different number of times. For example, once, twice, three times etc. Once the pulse generator 170 is programmed to a particular state, it supplies stimulation pulses to the vagus nerve 54 according to the programmed state, until stimulation energy is received from the inductively coupled part of the system 68. When energy is received from inductively coupled part of the system 68, the battery operated portion goes into "sleep mode" for a predetermined period of time which is programmed.

FIG. 53 shows a representative digital circuitry used for the basic state machine circuit. The circuit consists of a PROM 322 that has part of its data fed back as a state address. Other address lines 329 are used as circuit inputs, and the state machine changes its state address on the basis of these inputs. The clock 323 is used to pass the new address to the PROM 322 and then pass the output from the PROM 322 to the outputs and input state circuits. The two latches 324, 325 are operated 180^0 out of phase to prevent glitches from unexpectedly affecting any output circuits when the ROM changes state. Each state responds differently according to the inputs it receives.

Thus, in this embodiment the functioning of the system is similar to as described earlier. This embodiment though is cheaper to produce and offers limited programmability of the battery operated part of the system.

While the invention herein disclosed has been described by means of specific embodiments and applications thereof, numerous modifications and variation could be made thereto by those skilled in the art without departing from the scope of the invention set forth in the claims.